

General

Guideline Title

BCSH guideline for the use of anti-D immunoglobulin for the prevention of haemolytic disease of the fetus and newborn.

Bibliographic Source(s)

Qureshi H, Massey E, Kirwan D, Davies T, Robson S, White J, Jones J, Allard S. BCSH guideline for the use of anti-D immunoglobulin for the prevention of haemolytic disease of the fetus and newborn. *Transfus Med*. 2014 Feb;24(1):8-20. [47 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Parker J, Wray J, Gooch A, Robson S, Qureshi H. Guidelines for the use of prophylactic anti-D immunoglobulin. London (UK): British Committee for Standards in Haematology (BCSH); 2006. 13 p. [21 references]

Recommendations

Major Recommendations

Note from the British Committee for Standards in Haematology (BCSH) and the National Guideline Clearinghouse (NGC): The BCSH has released an amendment to the original guideline document that discusses anti-D prophylaxis in overweight women and provides a clarification of the recommendations regarding anti-D prophylaxis following intrauterine death (IUD). See the "Availability of Companion Documents" for further information.

Definitions for the quality of the evidence (A–C) and strength of recommendations (Strong [Grade 1], Weak [Grade 2]) are given at the end of the "Major Recommendations" field.

Potentially Sensitising Events Requiring Anti-D Immunoglobulin (Anti-D Ig) Prophylaxis

Following potentially sensitising events, anti-D Ig should be administered as soon as possible and always within 72 h of the event. If, exceptionally, this deadline has not been met some protection may be offered if anti-D Ig is given up to 10 days after the sensitising event (Grade 1C).

Potentially Sensitising Events in Pregnancies of Less Than 12 Weeks of Gestation

In pregnancies <12 weeks gestation, anti-D Ig prophylaxis (minimum dose 250 IU) is only indicated following an ectopic pregnancy, molar pregnancy, therapeutic termination of pregnancy and in some cases of uterine bleeding where this is repeated, heavy or associated with abdominal pain. A test for fetomaternal haemorrhage (FMH) is not required (Grade 2C).

Potentially Sensitising Events in Pregnancies of 12 Weeks to Less Than 20 Weeks Gestation

For potentially sensitising events between 12 and 20 weeks gestation a minimum dose of 250 IU should be administered within 72 h of the event. A test for FMH is not required (Grade 2C).

Potentially Sensitising Events in Pregnancies of 20 Weeks of Gestation to Term

- For potentially sensitising events after 20 weeks gestation a minimum anti-D Ig dose of 500 IU should be administered within 72 h of the event (Grade 2C).
- Appropriate tests for FMH should be carried out for all D negative, previously non-sensitised, pregnant women who have had a potentially sensitising event after 20 weeks of gestation, and additional dose(s) of anti-D Ig should be administered as necessary (Grade 1C).

Routine Antenatal Anti-D Prophylaxis (RAADP)

- All D negative pregnant women who have not been previously sensitised should be offered routine RAADP either with a single dose regimen given around 28 weeks, or two dose regimen given at around 28 and 34 weeks (Grade 1B).
- It is important that the 28-week sample for blood group and antibody screen is taken prior to the first routine prophylactic anti-D Ig injection being given. This forms the second screen required in pregnancy as stated in the British Committee for Standards in Haematology (BCSH) Guidelines for Blood Grouping and Red Cell Antibody Testing during pregnancy (Grade 2C).
- The RAADP scheme should be regarded as supplementary to any anti-D Ig administered for sensitising episodes listed in Table 1 in the original guideline document (Grade 2C).

Prophylaxis Following Birth of a D Positive Child or Intrauterine Death

- Following birth, ABO and rhesus (Rh) D typing should be performed on cord blood sample and if the baby is confirmed to be D positive, all D negative, previously non-sensitised, women should receive at least 500 IU of anti-D Ig within 72 h following delivery. Maternal samples should be tested for FMH and additional dose(s) given as guided by FMH tests (Grade 1B).
- If there is an intrauterine death (IUD) and hence no sample can be obtained from the baby, prophylactic anti-D Ig should be administered to D negative, previously non-sensitised women. A minimum of 500 IU of anti-D Ig should be administered within 72 h following the diagnosis of IUD. Maternal samples should be tested for FMH and additional dose(s) given as guided by FMH tests. It should be noted that the diagnosis of IUD is the sensitising event rather than delivery and hence anti-D Ig should be administered within 72 h of diagnosis (Grade 2C).
- If cord blood sample cannot be obtained or if cord blood group cannot be established for any reason, at least 500 IU anti-D Ig should be administered to D negative, previously non-sensitised women (Grade 2C).
- Where intra-operative cell salvage (ICS) is used during Caesarean section in D negative, previously non-sensitised women, and where cord blood group is confirmed as D positive (or unknown), a minimum dose of 1500 IU anti-D Ig should be administered following the re-infusion of salvaged red cells, and a maternal sample should be taken for estimation of FMH 30 to 45 min after reinfusion in case more anti-D Ig is indicated. It is important that clinicians inform the transfusion laboratory if ICS has been used to ensure that correct dose of anti-D Ig is issued (Grade 2C).

Principles, Safety, Availability, Dosage and Administration of Anti-D Ig

- Adequate records of issue and administration should be maintained to allow full traceability of anti-D immunoglobulin (Grade 2C).
- Where anti-D is detected in a sample from a pregnant woman, further history should be obtained and investigations undertaken to establish whether this is immune or passive. If no clear conclusion can be reached as to the origin of anti-D, then prophylaxis should continue to be administered in accordance with guidelines for D negative women who have not formed immune anti-D (Grade 2C).

Definitions:

Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what is known or is certain.

(A) High: Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate: Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g., inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a

dose–response gradient).

(C) Low: Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

Strength of Recommendations

Strong (Grade 1): Strong recommendations (Grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as "recommend".

Weak (Grade 2): Where the magnitude of benefit or not is less certain a weaker Grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as "suggest".

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Haemolytic disease of the fetus and newborn (HDN)

Guideline Category

Management

Prevention

Treatment

Clinical Specialty

Family Practice

Hematology

Internal Medicine

Obstetrics and Gynecology

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

- To provide healthcare professionals with practical guidance on the use of anti-D immunoglobulin (anti-D Ig) as immunoprophylaxis to

prevent sensitisation to the D antigen during pregnancy or at delivery for the prevention of haemolytic disease of the fetus and newborn (HDN)

- To ensure concordance with other British Committee for Standards in Haematology (BCSH) guidelines including guidelines for estimation of fetomaternal haemorrhage (FMH), blood grouping and antibody testing in pregnancy and recently published compatibility procedures in blood transfusion laboratories as well as professional guidelines produced by the Royal College of Obstetrics and Gynaecologists

Target Population

- Previously non-sensitised, D negative women during pregnancy, following delivery or termination of pregnancy, or following intrauterine death
- D negative girls or women of child bearing potential who are given D positive blood components

Interventions and Practices Considered

1. Administration of anti-D immunoglobulin (anti-D Ig) as soon as possible after potentially sensitising events
2. Anti-D Ig prophylaxis (following an ectopic pregnancy, molar pregnancy, therapeutic termination of pregnancy and in some cases of uterine bleeding)
3. Appropriate testing for fetomaternal haemorrhage (FMH)
4. Routine antenatal prophylaxis with anti-D Ig (RAADP)
5. Performing 28-week sample for blood group and antibody screen prior to first routine prophylactic anti-D Ig injection
6. Performing ABO and rhesus (Rh) D typing on cord blood following birth
7. Anti-D Ig prophylaxis in the event of a D positive child or intrauterine death
8. Maintenance of auditable records of issue and administration to allow full traceability of anti-D Ig
9. Investigation performed when anti-D is detected in a blood sample from a pregnant woman to establish whether this is immune or passive

Major Outcomes Considered

- Sensitisation rate
- Morbidity and mortality

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

A search of published literature was undertaken using the Cochrane Library, PubMed, MEDLINE, EMBASE and internet searches using the following key words and relevant MeSH terms: anti D, anti-D Ig immune globulin, pregnancy, antenatal, prophylaxis, rhesus, Rh D, Rh D haemolytic disease, erythroblastosis fetalis. This search covered the period 1999 to March 2013 and was limited to the English language and humans.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Rating Scheme for the Strength of the Evidence

Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what is known or is certain.

(A) High: Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate: Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g., inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low: Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

Methods Used to Analyze the Evidence

Systematic Review

Description of the Methods Used to Analyze the Evidence

The papers included were subjected to critical reading by the authors using the Critical Appraisal Skills Programme (CASP) appraisal tool and were ranked according to the hierarchy of evidence (see the "Rating Scheme for the Strength of the Evidence" field). This approach took account of the National Institute for Health and Care Excellence (NICE) systematic review undertaken in 2000, and the NICE Health Technology Assessment report published in 2007.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

This guideline was developed in accordance with the standard British Committee for Standards in Haematology (BCSH) methodology for producing BCSH guidelines. The guideline group was selected to be representative of medical and scientific UK-based experts.

The writing group produced the draft guideline, which was subsequently revised by consensus by members of the Transfusion Task Force of the British Committee for Standards in Haematology.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Strong (Grade 1): Strong recommendations (Grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as "recommend".

Weak (Grade 2): Where the magnitude of benefit or not is less certain a weaker Grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as "suggest".

Cost Analysis

The guideline developers reviewed published cost analyses.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The guideline was reviewed by a sounding board of United Kingdom (UK) haematologists, the British Committee for Standards in Haematology (BCSH) and the British Society for Haematology (BSH) Committee as well as representatives from the Royal College of Obstetrics and Gynaecology and the Royal College of Midwifery, with comments incorporated where appropriate.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field.)

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of anti-D immunoglobulin (anti-D Ig) for the prevention of haemolytic disease of the fetus and newborn (HDN)

Potential Harms

- The manufacturing process for anti-D immunoglobulin (anti-D Ig) preparations includes viral inactivation steps in order to further reduce the risk of viral transmission. The theoretical risk of transmission of variant Creutzfeldt-Jakob disease (vCJD) remains unquantifiable, though is likely to be extremely small.
- Product safety data submitted by manufacturers to inform National Institute of Health and Clinical Excellence technical appraisal guidance 156 (NICE, 2002, 2008) indicates a very low rate of reporting a probable or possible adverse event, estimated to be less than one event per 80,000 doses of anti-D Ig. The majority of reported adverse events were not considered serious. There is no evidence to suggest that anti-D Ig administered to women during pregnancy is harmful to the fetus.
- Allergic reactions are very rare but severe hypersensitivity including anaphylaxis may occur. Anti-D preparations may contain trace amounts of immunoglobulin A (IgA) (less than $5 \mu\text{g mL}^{-1}$) and hence patients with known antibodies to IgA have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. If symptoms of allergic or early signs of hypersensitivity reactions (including generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis) develop, administration of anti-D must be discontinued immediately and appropriate treatment instituted. Manufacturer's prescribing information for Rhophylac® recommends that medication such as adrenaline should be available for immediate treatment of acute severe hypersensitivity reactions.
- When more than one unit of D positive blood has been inadvertently transfused to D negative women, a red cell exchange transfusion should be considered to reduce the load of D positive red cells in the circulation and the dose of anti-D Ig required to prevent immunisation. In this situation advice should be sought from a specialist in transfusion medicine, and the patient should be counselled regarding the implications of both non-intervention (for future pregnancies) and of treatment, including any hazards from receiving donated blood, the exchange procedure itself and of larger doses of anti-D Ig, including intravenous (IV) anti-D Ig.
- It should be noted that due to the nature of the manufacturing process, D-GAM® preparations are suitable for intramuscular (IM) USE

ONLY and therefore *must not* be administered IV because of the risk of severe hypersensitivity reactions due to the presence of trace amounts of IgA and other plasma proteins.

- When large or multiple doses of anti-D Ig are necessary, consideration should be given to limiting batch exposure whenever possible, for example, reserving the same anti-D Ig batch for routine antenatal anti-D prophylaxis (RAADP) and the postnatal dose, but this should not in any way delay the timely provision of anti-D Ig.
- The deltoid muscle is an appropriate and safe site for IM administration of anti-D Ig. If the gluteal region is used, particular care should be taken to ensure that the injection is given into muscle, as absorption may be delayed if it only reaches the subcutaneous tissues. In women with severe thrombocytopenia (platelet count $\leq 30 \times 10^9/L$) or a history of a bleeding disorder such as severe Von Willebrand disease, anti-D Ig should be administered IV or subcutaneously depending on whether a preparation suitable for IV use is available. Women with significant bleeding disorders such as Von Willebrand disease should be managed jointly with a haemophilia centre.
- The risk of a false negative result (i.e., missing an D positive fetal blood group) in fetal blood group genotyping using cell free fetal deoxyribonucleic acid (cffDNA) from maternal blood samples taken at 16 to 20 week gestation is small and currently estimated to be around 0.08 to 0.16% according to one study.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Audit Criteria/Indicators

Chart Documentation/Checklists/Forms

For information about availability, see the *Availability of Companion Documents and Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Staying Healthy

IOM Domain

Effectiveness

Safety

Timeliness

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

1999 (revised 2014 Feb)

Guideline Developer(s)

British Committee for Standards in Haematology - Professional Association

Source(s) of Funding

British Committee for Standards in Haematology

Guideline Committee

British Committee for Standards in Haematology (BCSH) Writing Group

Composition of Group That Authored the Guideline

Writing Group Members: H. Qureshi, Department of Haematology, University Hospitals of Leicester, Leicester, UK; E. Massey, NHS Blood & Transplant, Bristol, UK; D. Kirwan, NHS Fetal Anomaly Screening Programme, UK National Screening Committee, University of Exeter, Exeter, UK; T. Davies, NHS Blood & Transplant, Manchester, UK; S. Robson, Department of Fetal Medicine, Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK; J. White, UKNEQAS Blood Transfusion Laboratory Practice, West Hertfordshire Trust, Hertfordshire, UK; J. Jones, Welsh Blood Service, Pontyclun, UK; S. Allard, NHS Blood and Transplant, London, UK

Financial Disclosures/Conflicts of Interest

None of the authors have declared a conflict of interest.

Guideline Status

This is the current release of the guideline.

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Guideline Availability

Electronic copies: Available from the [Transfusion Medicine Web site](#) .

Print copies: Available from the British Committee for Standards in Haematology; Email: bcsh@b-s-h.org.uk.

Availability of Companion Documents

The following are available:

- BCSH guideline for the use of anti-D immunoglobulin for the prevention of haemolytic disease of the fetus and newborn. Appendix 2: SHOT flowchart to guide the appropriate administration of anti-D Ig. Anti-D administration checklist. British Committee for Standards in Haematology (BCSH); 2012 Oct. 1 p. Electronic copies: Available from the [British Committee for Standards in Haematology \(BCSH\) Web site](#) .
- BCSH anti-D guidelines 2014 – amendment 4.8.14. British Committee for Standards in Haematology (BCSH); 2014. 2 p. Electronic topics: Available from the [BCSH Web site](#) .

In addition, suggested standards for clinical audit are available in Section 10 of the [original guideline document](#) .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on May 27, 2008. The information was verified by the guideline developer on June 30, 2008. This summary was updated by ECRI Institute on April 30, 2014.

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